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(21) International Application Number: PCT/GB96/00490 (22) International Filing Date: 1 March 1996 (01.03.96) (30) Priority Data: 9504265.1 3 March 1995 (03.03.95) GB (71) Applicant (for all designated States except US): MEDEVA PLC [GB/GB]; 10 St. James's Street, London SW1A 1EP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): JONES, Julie, Irene [GB/GB]; 56 Townsend Lane, Harpenden, Hertfordshire AL5 2RG (GB). BAKER, Anthony, Richard [GB/GB]; Pucks Oak, Nightingale Avenue, West Horsley, Surrey KT24 6PB (GB). HALLS, Neil, Graham [AU/AU]; 31 Staldeford Avenue, Glen Waverley, VIC 3150 (AU). WATMOUGH, Peter [GB/GB]; 39 Amesbury Avenue, Grimsby, South Humberside DN33 3HT (GB). MARRIOTT, Peter [GB/GB]; 7 Fortuna Way, Grimsby, South Humberside DN37 9SH (GB). (74) Agents: HUTCHINS, Michael, Richard et al.; Fry Heath & Spence, The Old College, 53 High Street, Horley, Surrey RH6 7BN (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> BEST AVAILABLE COPY
(54) Title: CORTICOSTEROID-CONTAINING PHARMACEUTICAL COMPOSITION (57) Abstract The present invention provides a foamable pharmaceutical composition comprising a corticosteroid active substance, a quick-break foaming agent, a propellant and a buffering agent. The quick-break foaming agent typically comprises an aliphatic alcohol, water, a fatty alcohol and surface active agent. The compositions of the invention can be used to treat various skin disease, and in particular scalp psoriasis.		

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CORTICOSTEROID-CONTAINING PHARMACEUTICAL COMPOSITION

The present invention relates to an improved composition for the topical application of corticosteroid active substances to the skin of a subject.

Corticosteroids, particularly in the form of the ester compounds, are used, inter alia, in the treatment of skin diseases in humans, such as eczema, infantile eczema, atopic dermatitis, dermatitis herpetiformis, contact dermatitis, seborrhoeic dermatitis, neurodermatitis, psoriasis and intertrigo. Formulations containing such active substances have conventionally been applied to the skin site in the form of alcoholic solutions, lotions or creams. However, there is a high degree of ineffectiveness with such formulations. Lotions and creams are generally too viscous to allow efficient penetration of the active to the epidermis, and solutions have a tendency to evaporate before penetrating the epidermis. In addition, conventional cream bases are irritating to the skin, particularly over the often long exposure that is required, and the fluidity of lotions often makes the physical application difficult to control. Moreover, it is necessary to rub such formulations into the target site to improve the penetration of the active substance into the epidermis, an action which itself produces irritation.

There has therefore been a very real need in the treatment of skin disorders requiring treatment with corticosteroids for improved formulations which target the most effective corticosteroid to the skin site with improved delivery of active, with decreased inconvenience and irritation, and increased ease of use for the patient.

The present invention provides an improved composition which addresses this need.

In one aspect, the present invention provides a foamable pharmaceutical composition comprising a corticosteroid active substance, a quick-break foaming agent, a propellant and a buffering agent.

Such a composition is applied to the skin site (after foaming) as a foam which is a thermophobic (heat sensitive) quick-break foam. On application to the skin, the composition is initially in the form of a mousse-like foam. The quick-break foam slowly breaks down at the skin temperature to a liquid to allow the alcohol and active substance to saturate the treatment site. Such a system provides enhanced penetration of the alcohol and active substance through the epidermis. Because the composition is supplied as a mousse, the semi-rigid behaviour of the composite makes it easier to handle and physically control. The foamed composition, when applied, provides a thick ball of foam which disintegrates easily when spread, allowing proper coverage of the skin site to be treated without premature evaporation of the solvent. It has been found important to include a buffering agent in the composition to stabilize the active isomer of the corticosteroid active substance in the complex foamable composition, otherwise the complex interactions within the foamable composition may result in the instability of the more active isomer.

Use of a quick-break foaming agent is required in the present invention. Such agents are known. Suitable quick-break foaming agents in the present invention are those described in Australian Patent No. 463216 and International Patent Application WO 85/01876. It is generally preferred that the quick-breaking foaming agent comprises an aliphatic alcohol, water, a fatty alcohol and a surface active agent. Particularly preferred is a quick-break foaming agent having the following composition:

- (a) an aliphatic alcohol, preferably in amounts of 40-90% w/w composition, more preferably 55-70% w/w, especially 57-59% w/w;
- (b) water, preferably in amounts of 10-40% w/w;
- (c) at least one fatty alcohol, preferably in amounts of 0.5-10% w/w; and
- (d) a surface active agent, preferably an ethoxylated sorbitan ester (as emulsifier), typically in amounts of 0.1-15% w/w.

In the quick-break foaming agent, the fatty alcohol may be chosen from, for example, cetyl, stearyl, lauryl, myristyl and palmityl alcohols and mixtures of two or more thereof. Mixtures of cetyl alcohol and a stearyl alcohol such as octadecan-1-ol have been found to be particularly preferred; the ratio between these two components may be adjusted to maintain foam viscosity throughout the broadest possible temperature range. In this situation, the stearyl alcohol maintains the viscosity at temperatures above 20°C whilst cetyl alcohol maintains the viscosity below 20°C.

The aliphatic alcohol may preferably be chosen from methyl, ethyl, isopropyl and butyl alcohols, and mixtures of two or more thereof. Ethanol has been found to be particularly preferred.

Surface active agents utilised in the quick-break foaming agent may preferably be chosen from ethoxylated sorbitan stearate, palmitate, oleate, nonyl phenol ethoxylates and fatty alcohol ethoxylates, and mixtures of two or more thereof. Thus, for example, Polysorbate 60 (a mixture of partial stearic esters of sorbitol and its anhydrides copolymerised with approximately 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides) has been found to be particularly preferred. The surface active agent enhances the fatty alcohol solubility in the system and enhances foam formation.

The propellant used may be chosen from conventional aerosol propellants. Thus, one may select the propellant from propane, butane, dichloro difluoro methane, dichloro tetrafluoro ethane, octafluoro cyclobutane, and mixtures of two or more thereof. It is necessary to select a propellant most compatible with the entire system. It is particularly preferred that the propellant be present in amounts preferably of 3-30% w/w, more preferably 3-10%w/w, especially 3-5% w/w. The maximum level of propellant will be determined as the amount miscible with the utilized water/aliphatic alcohol ratio. In addition to acting as a propellant, the propellant will also act as a solvent for the fatty acids and active substances in the aqueous/alcoholic system.

It is possible that other additives may be used. Thus, it is preferred to add a humectant to reduce the drying effects of the aqueous aliphatic alcohol. Such a humectant may preferably be present in an amount of 0.1-10.0% w/w, more preferably 0.5-3.0% w/w. It is particularly preferred that the humectant be propylene glycol, but other humectants such as glycerine, panthenol and sorbitol may be used.

The composition of the present invention may be used to deliver corticosteroid compounds which have utility in the topical treatment of skin disorders. Thus, for example, the composition of the present invention may be used to deliver the following topically-effective corticosteroids:

alclometasone dipropionate	fluclorolone acetonide
amcinonide	fluocinolone acetonide
beclamethasone dipropionate	fluocinonide
betamethasone benzoate	fluocortin butyl
betamethasone dipropionate	fluocortolone preparations
betamethasone valerate	fluprednidene acetate
budesonide	flurandrenolone
clobetasol propionate	halcinonide

clobetasone butyrate	hydrocortisone
desonide	hydrocortisone acetate
desoxymethasone	hydrocortisone butyrate
diflorasone diacetate	methylprednisolone acetate
diflucortolone valerate	mometasone furoate
flumethasone pivalate	triamcinolone acetonide

and pharmacologically effective mixtures thereof.

Compositions according to the invention are especially advantageous for the topical administration to the skin of human subjects of betamethasone and its derivatives such as betamethasone benzoate, betamethasone dipropionate, and betamethasone valerate. It is particularly preferred to use the valerate ester, especially in the treatment of psoriasis.

The corticosteroid active substance is preferably present in an amount of 0.01-1.0% w/w more preferably 0.05-0.2% w/w.

In view of the complexity of the composition, it has been found that unexpectedly in order to ensure stability of the active isomer of the corticosteroid in the composition and thus to ensure delivery of the most active isomer to the epidermis, it is necessary to buffer the composition by including a suitable buffering agent. Suitable buffering agents are acetic acid/sodium acetate, citric acid/sodium citrate and phosphoric acid/sodium phosphate, and it is desirable generally to buffer the composition to pH 3.0-6.0, preferably 4.0-5.0 and to this end the buffering agent may preferably be present in an amount of 0.01-1.0% w/w, more preferably 0.05-0.2% w/w. It is particularly preferred to use a citrate buffer system, more preferably anhydrous citric acid/potassium citrate, to buffer the composition to pH 4.5, when betamethasone valerate is used as the active substance; in this case citrate buffering stabilises the more active 17-

valerate ester over the less active 21-valerate ester in the complex composition and ensures that the most effective form of the active substance is efficiently delivered to the epidermis.

Preparation of the composition may be effected by conventional means so as to produce a homogeneous solution of fatty alcohol(s) (wax[es]) in an alcohol/water base. The relative proportions of the fatty alcohol(s), water/aliphatic alcohol and propellant are conveniently controlled according to conventional means so as to provide a homogeneous clear solution and so as to provide a homogeneous clear solution and so as to allow the formation of a suitable quick-break foam. Generally speaking the fatty alcohol(s), surface active agent, aliphatic alcohol and humectant (if present) are preferably mixed together with the corticosteroid active substance to produce an "Alcohol Phase". An "Aqueous Phase" is preferably produced by mixing the buffering agent and water. These phases are then mixed, preferably in the final container, in the required amounts. The propellant is then added under pressure to produce the composition according to the invention.

In the case of betamethasone valerate, for example, it is particularly preferred to use a composition comprising cetyl alcohol and octadecan-1-ol as fatty alcohols, together with Polysorbate 60 surface active agent, with purified water and ethanol as the aliphatic alcohol. The system is preferably buffered with anhydrous citric acid/potassium citrate and the propellant is preferably butane/propane. It is generally preferred to choose the proportion of the components to achieve a fixed pressure in the container of around 50-70 psi.

The composition of the present invention may be contained in and dispensed from a container capable of withstanding the pressure of the propellant gas and having an appropriate valve/nozzle for dispensing the composition as a foam under pressure. If the container is made of a metal

material likely to suffer corrosion under the action of the composition, the composition may include a corrosion inhibitor as an additive. Thus, the presence of a corrosion inhibitor may be necessary if the container is made of tin plate. Suitable corrosion inhibitors include organic acid salts, preferably chosen from sorbic acid, benzoic acid, sodium benzoate and potassium sorbate. If used, the corrosion inhibitor may be present in amounts of 0.1-15% w/w, more preferably 0.1-3% w/w. In the present invention, aluminium cans are preferred as containers, particularly when utilising the above-mentioned composition for betamethasone valerate as the corticosteroid active substance; in this case there is no corrosion problem and there is no need for the inclusion of a corrosion inhibiting agent.

In use, the composition is sprayed, producing a semi-solid form (a foam or mousse) which is suitable for the topical application to the site of interest, eg the scalp when treating dermatological conditions of the scalp. On application, heat from the skin causes the mousse to break down into liquid form, thus releasing the aliphatic alcohol and corticosteroid active substance which penetrate the skin site, leaving a low amount of residue, many times lower than those obtained when delivering active from a cream base. This route of administration facilitates the ease of specific local application, and the composition according to the invention provides a convenient, controllable and efficient vehicle for delivering topically active corticosteroids to the skin. This gives greater physical control compared to conventional topical corticosteroid formulations, minimises rubbing of the target site and allows the alcoholic vehicle to penetrate the skin to deliver the active to where it will have the greatest effect.

The composition of the present invention may be used in treating skin diseases which are conventionally treated with corticosteroid active substances. Thus, the composition may be used in the treatment of, inter alia, eczema, infantile eczema, atopic dermatitis, dermatitis herpetiformis, contact dermatitis, seborrhoeic dermatitis, neurodermatitis, psoriasis and

intertrigo. The composition is especially useful in the treatment of scalp psoriasis in human subjects.

The present invention will now be illustrated by means of the following non-limiting Example:

EXAMPLE

Betamethasone valerate composition

A betamethasone valerate formulation having the following composition was prepared:

	<u>% w/w</u>
Betamethasone Valerate	0.12
Cetyl Alcohol BP	1.10
Octadecan-1-ol BP	0.50
Polysorbate 60 BP	0.40
Ethanol	57.79
Purified Water	33.69
Propylene Glycol BP	2.00
Citric Acid Anhydrous BP	0.073
Potassium Citrate	0.027
Butane/Propane	4.30

	100.00

Cetyl alcohol (HYFATOL 1698, EfKay Chemicals Limited, London), octadecan-1-ol (HYFATOL 1898, EfKay Chemicals Limited, London), Polysorbate 60 (CRILLET 3, Croda Chemicals, North Humberside) and ethanol in the correct proportions were mixed and heated to about 45°C,

with continuous stirring until the mix became clear. Betamethasone valerate BP (Roussel Uclaf, Virtolaye, France) was slowly transferred into the mix, again with continuous stirring until the mix became clear. (Alcoholic Phase)

Purified water was separately heated to 45°C and anhydrous citric acid BP and potassium citrate BP transferred to the water, with continuous stirring until dissolved. (Aqueous Phase)

The Alcoholic and Aqueous phases were each filtered through 75 micron screens and the required weights filled into a can (aluminium, epoxy lined) at room temperature. After attaching a valve, the butane/propane propellant (Propellant P70) was added to the mix in the can to the required weight, and an actuator added to the valve.

The composition, on being sprayed from the can onto the skin, produces a thermophobic foam which breaks down under heating from the skin to release the active to the epidermis. The presence of the citrate buffer stabilizes the 17-valerate configuration of the betamethasone valerate over the less active 21-valerate configuration, thus producing a composition which efficaciously delivers active to the epidermis and which is particularly suitable for the treatment of psoriasis, especially scalp psoriasis.

CLAIMS

1. A foamable pharmaceutical composition comprising a corticosteroid active substance, a quick-break foaming agent, a propellant and a buffering agent.
2. A foamable pharmaceutical composition comprising a quick-break foaming agent, a propellant, a buffering agent, and a corticosteroid active substance, the corticosteroid steroid active substance being of a type which exhibits isomerism and has a more active isomer and a less active isomer, the corticosteroid active substance being present as the more active isomer, and the buffering agent being present in an amount effective to stabilise the more active isomer against isomerisation to the less active isomer.
3. A foamable pharmaceutical composition according to Claim 1 or Claim 2 which is buffered to a pH in the range 3.0 to 6.0.
4. A foamable pharmaceutical composition according to Claim 3 which is buffered to a pH in the range 4.0 to 5.0.
5. A foamable pharmaceutical composition according to any one of the preceding Claims wherein the buffering agent is present in an amount from 0.01 to 1.0% w/w.
6. A foamable pharmaceutical composition according to Claim 5 wherein the buffering agent is present in an amount in the range 0.05 to 0.2% w/w.
7. A foamable pharmaceutical composition according to any one of the preceding Claims wherein the buffering agent is selected from acetic acid/sodium acetate buffer, citric acid/sodium citrate

buffer and phosphoric acid/sodium phosphate buffer.

8. A foamable pharmaceutical composition according to any one of the preceding Claims wherein the corticosteroid active substance is a topically effective corticosteroid selected from:

alclometasone dipropionate	flucilorolone acetonide
amcinonide	fluocinolone acetonide
beclamethasone dipropionate	fluocinonide
betamethasone benzoate	fluocortin butyl
betamethasone dipropionate	fluocortolone preparations
betamethasone valerate	fluprednidene acetate
budesonide	flurandrenolone
clobetasol propionate	halcinonide
clobetasone butyrate	hydrocortisone
desonide	hydrocortisone acetate
desoxymethasone	hydrocortisone butyrate
diflorasone diacetate	methylprednisolone acetate
difluocortolone valerate	mometasone furoate
flumethasone pivalate	triamcinolone acetonide

and pharmacologically effective mixtures thereof.

9. A foamable pharmaceutical composition according to any one of the preceding Claims wherein the corticosteroid active substance is betamethasone or a derivative thereof.
10. A foamable pharmaceutical composition according to Claim 9 wherein the corticosteroid active substance is selected from betamethasone benzoate, betamethasone dipropionate and betamethasone valerate.
11. A foamable pharmaceutical composition according to Claim 10 wherein the corticosteroid active substance is betamethasone valerate.

12. A foamable pharmaceutical composition according to any one of the preceding Claims wherein the corticosteroid active substance is present in an amount from 0.01 to 1.0% w/w.
13. A foamable pharmaceutical composition according to Claim 12 wherein the corticosteroid active substance is present in an amount from 0.5 to 0.2% w/w.
14. A foamable pharmaceutical composition according to any one of the preceding Claims wherein the quick-break foaming agent comprises an aliphatic alcohol, water, a fatty alcohol and a surface active agent.
15. A foamable pharmaceutical composition according to Claim 14 wherein the aliphatic alcohol is present in an amount corresponding to 40 to 90% by weight of the total weight of the composition.
16. A foamable pharmaceutical composition according to Claim 15 wherein the aliphatic alcohol is present in an amount corresponding to 55 to 70% by weight of the composition.
17. A foamable pharmaceutical composition according to Claim 16 wherein the aliphatic alcohol is present in an amount corresponding to 57 to 59% by weight of the composition.
18. A foamable pharmaceutical composition according to any one of Claims 14 to 17 wherein the aliphatic alcohol is selected from methanol, ethanol, isopropyl alcohol, and butyl alcohol and mixtures of two or more thereof.
19. A foamable pharmaceutical composition according to Claim 18 wherein the aliphatic alcohol is ethanol.

20. A foamable pharmaceutical composition according to any one of Claims 14 to 19 wherein the water is present in an amount in the range 10 to 40% by weight of the composition.
21. A foamable pharmaceutical composition according to any one of Claims 14 to 20 wherein the fatty alcohol is present in an amount corresponding to 0.5 to 10% by weight of the composition.
22. A foamable pharmaceutical composition according to any one of Claims 14 to 21 wherein the fatty alcohol is selected from cetyl, stearyl, lauryl, myristyl and palmityl alcohols and mixtures of two or more thereof.
23. A foamable pharmaceutical composition according to Claim 22 wherein the fatty alcohol is a mixture of cetyl alcohol and a stearyl alcohol.
24. A foamable pharmaceutical composition according to any one of Claims 14 to 23 wherein the surface active agent is present in an amount from 0.1 to 15% w/w of the composition.
25. A foamable pharmaceutical composition according to any one of Claims 14 to 24 wherein the surface active agent is selected from an ethoxylated sorbitan stearate, palmitate, oleate, nonyl phenol or fatty alcohol, and mixtures of two or more thereof.
26. A foamable pharmaceutical composition according to Claim 25 wherein the surface active agent is a mixture of partial stearic esters of sorbitol and its anhydrides copolymerised with approximately 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides.
27. A pharmaceutical product comprising a foamable pharmaceutical composition according to any one of the preceding Claims contained

within a container capable of withstanding the pressure of the propellant gas, and having a valve or nozzle for dispensing the foamable composition as a foam under pressure.

28. A foamable pharmaceutical composition according to Claim 1 having the following composition:

	<u>% w/w</u>
Betamethasone Valerate	0.12
Cetyl Alcohol BP	1.10
Octadecan-1-ol BP	0.50
Polysorbate 60 BP	0.40
Ethanol	57.79
Purified Water	33.69
Propylene Glycol BP	2.00
Citric Acid Anhydrous BP	0.073
Potassium Citrate	0.027
Butane/Propane	4.30

	100.00

29. A foamable pharmaceutical composition according to any one of Claims 1 to 27, or a pharmaceutical product according to Claim 28, for use in the treatment of eczema, infantile eczema, atopic dermatitis, dermatitis herpetiformis, contact dermatitis, seborrhoeic dermatitis, neurodermatitis, psoriasis and intertrigo.
30. A foamable pharmaceutical composition or pharmaceutical product according to claim 29 for use in the treatment of scalp psoriasis.
31. A method of treatment of a skin disease susceptible to treatment with corticosteroid active substances, which method comprises administering topically to a patient in need thereof an effective

amount of a foamable pharmaceutical composition as defined in any one of Claims 1 to 26, or a pharmaceutical product as defined in Claim 27.

32. A method according to Claim 31 wherein the skin disease is selected from eczema, infantile eczema, atopic dermatitis, dermatitis herpetiformis, contact dermatitis, seborrhoeic dermatitis, neurodermatitis, psoriasis and intertrigo.
33. A method according to Claim 32 for treating scalp psoriasis in human subjects.

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/GB 96/00490

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/57 A61K9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 484 530 (HISAMITSU PHARMACEUTICAL) 13 May 1992 see claims 1-3 see page 3, line 40 - page 4, line 50 ---	1-33
A	US,A,4 018 918 (THE UPJOHN COMPANY) 19 April 1977 see claim 1 see column 11, line 3 - column 12, line 11 ---	1-33
A	EP,A,0 423 695 (STERLING DRUG) 24 April 1991 see claims 1,2 see page 2, line 50 - page 4, line 6 --- -/--	1-33

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

*** Special categories of cited documents :**

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- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *A* document member of the same patent family

Date of the actual completion of the international search

10 June 1996

Date of mailing of the international search report

21.06.96

Name and mailing address of the ISA

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Authorized officer

Ventura Amat, A

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/GB 96/00490

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO,A,85 01876 (LOCKLEY SERVICES) 9 May 1985 cited in the application see claims 1-16 -----</p>	1-33

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB96/00490

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 29-33 are directed to a method of treatment of the
human body the search has been carried out and based on the alleged
effects of the composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such
an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 96/00490

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-484530	13-05-92	DE-D- 69020900	17-08-95
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		US-A- 5378451	03-01-95
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